Clinical trial results:
Preparation and application of autologous immunohybridoma cells for the treatment of prostate cancer

Summary

EudraCT number	2012-005498-29
Trial protocol	SI
Global end of trial date	08 November 2016

Results information

Result version number	v1 (current)
This version publication date	06 May 2020
First version publication date	06 May 2020
Summary attachment (see zip file)	Results summary (Results_summary.pdf)

Trial information

Trial identification

Sponsor protocol code	2.28

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celica Biomedical
Sponsor organisation address	Tehnološki park 24, Ljubljana, Slovenia, 1000
Public contact	Clinical trial information desk , Celica Biomedical, 386 (0)1544 36 04, office@celicabiomedical.com
Scientific contact	Clinical trial information desk, Celica Biomedical, 386 (0)1544 36 04, robert.zorec@celica.si

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 November 2016
Global end of trial reached?	Yes
Global end of trial date	08 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Main objectives of the trial were to assess safety, feasibility, tolerability and non-toxicity of the treatment with autologous dendritic-tumor hybridoma cells and the effect on the quality of live of the patients with castration resistant prostate cancer.

Protection of trial subjects:

Prostate biopsy samples were taken under local anesthesia (10 mL of 2% xylocaine periprostatic injection, plus intrarectal application of 10 mL of 2% xylocaine jelly; both AstraZeneca, UK), using transrectal ultrasonography (B-K Medical, UltraView 800, USA), a biopsy gun with 18G needles (Magnum reusable biopsy gun; Bard Biopsy Systems, USA). The removal of prostate tumor tissue did not cause pain or other side effects or inconvenience to the patients. All patients received per oral ciprofloxacin prophylaxis (2 × 500 mg daily for 5 days) and were advised not to perform major physical activity for a few days.

Background therapy:

continuous androgen-deprivation therapy
standard supportive therapy for prevention of skeleton-related events (ie, denosumab, once monthly)

Evidence for comparator: -

Actual start date of recruitment	03 February 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Scientific research
Long term follow-up duration	27 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Slovenia: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Dates of recruitment period: from February 2014 to January 2016
Territories: Slovenia

Pre-assignment

Screening details:

Histologically proven prostate cancer; Progressive disease; No signs of previous therapy toxicity; During the trial, patients should not receive chemotherapy treatment in parallel; Patients should be without corticosteroid; Not receiving any previous immunotherapy; Hormonal therapy permitted to maintain castration levels of testosterone.

Pre-assignment period milestones

Number of subjects started	22
Number of subjects completed	22

Period 1

Period 1 title	baseline period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Carer, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	aHyC

Arm description:

Received autologous hybridoma cell (aHyC) vaccine - first.

Arm type	Experimental
Investigational medicinal product name	autologous hybridoma cell vaccine
Investigational medicinal product code	aHyC
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each patient received four injections of aHyC vaccine at 3-week intervals. The number of cells in each vaccine varied with each patient, however, in all cases, these were the maximal numbers of autologous cells that could be obtained from the prostate tissue samples and leukocyte concentrates (median cell number per vaccine: 7.7 × 10'6).

Arm title	control

Arm description:

Received vaccine vehicle (placebo) - first.

Arm type	Placebo
Investigational medicinal product name	vaccine vehicle
Investigational medicinal product code	placebo
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:
Each patient received four injections of vaccine vehicle at 3-week intervals.

Number of subjects in period 1	aHyC	control
Started	12	10
Completed	12	9
Not completed	0	1
additional malignancy	-	1

Period 2	
Period 2 title	cross-over
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms	
Are arms mutually exclusive?	Yes
Arm title	aHyC

Arm description:
Received vaccine vehicle (placebo).

Arm type	Active comparator
Investigational medicinal product name	vaccine vehicle
Investigational medicinal product code	placebo
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:
Each patient received four injections of vaccine vehicle at 3-week intervals.

Arm title	control

Arm description:
Received autologous hybridoma cell (aHyC) vaccine.

Arm type	Active comparator
Investigational medicinal product name	autologous hybridoma cell vaccine
Investigational medicinal product code	aHyC
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each patient received four injections of aHyC vaccine at 3-week intervals. The number of cells in each vaccine varied with each patient, however, in all cases, these were the maximal numbers of autologous cells that could be obtained from the prostate tissue samples and leukocyte concentrates (median cell number per vaccine: 7.7 × 10'6).

Number of subjects in period 2	aHyC	control
Started	12	9
Completed	10	8
Not completed	2	1
Lost to follow-up	-	1
disease progression	2	-

Baseline characteristics

Reporting groups	
Reporting group title	aHyC
Reporting group description:	
Received autologous hybridoma cell (aHyC) vaccine - first.	

Reporting group title	control
Reporting group description:	
Received vaccine vehicle (placebo) - first.	

Reporting group values	aHyC	control	Total
Number of subjects	12	10	22
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	12	10	22
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	75.3	74.1	
standard deviation	± 5.7	± 7.6	-
Gender categorical			
All subjects were men.			
Units: Subjects			
Female	0	0	0
Male	12	10	22

End points

End points reporting groups

Reporting group title	aHyC
Reporting group description:	
Received autologous hybridoma cell (aHyC) vaccine - first.	

Reporting group title	control
Reporting group description:	
Received vaccine vehicle (placebo) - first.	

Reporting group title	aHyC
Reporting group description:	
Received vaccine vehicle (placebo).	
Reporting group title	control
Reporting group description:	
Received autologous hybridoma cell (aHyC) vaccine.	

Primary: Safety

End point title	Safety
End point description:	
Adverse events (AEs) were monitored during medical examinations.	
End point type	Primary
End point timeframe:	
Time-frame to observe adverse effects: from the first application in the first period until the start of the second period (cross-over) - to compare both arms.	

End point values	aHyC	control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: subjects				
Serious AE	0	0		
Mild AE	5	3		

Statistical analyses

Statistical analysis title	z-test of proportions
Comparison groups	aHyC v control

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.05
Method	z-test of proportions

Primary: Quality of life (QL)

End point title	Quality of life (QL)

End point description:

End point type	Primary

End point timeframe:

For the comparison of QL the evaluation period was set up to 4 months after the first application of aHyC vaccine or placebo. A t-test was used to compare QL between aHyC and placebo arm.

End point values	aHyC	control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	7		
Units: AU				
arithmetic mean (standard error)				
Quality of life	66.11 (± 6.02)	66.87 (± 3.68)		

Statistical analyses

Statistical analysis title	t-test

Statistical analysis description:

The mean quality of life score was calculated for up to 4 months after receiving first aHyC or placebo, for each patient who completed the questionnaire. From these data, the mean score in QL for aHyC and placebo arm was calculated, and the difference was tested with a 2-tailed t-test.

Comparison groups	aHyC v control
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Secondary: C-reactive protein

End point title	C-reactive protein

End point description:

End point type	Secondary

End point timeframe:

Values at the begging of the cross-over period are given for each arm. Baseline values for each arm were also different, but can not be inserted in this forms.

End point values	aHyC	control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	7		
Units: mg/l				
median (inter-quartile range (Q1-Q3))	2.2 (1.2 to 3.3)	0.8 (0.6 to 1.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum PSA

End point title	Serum PSA

End point description:

End point type	Secondary

End point timeframe:

Values at the begging of the cross-over period are given for each arm. Baseline values for each arm were also different, but can not be inserted in this forms.

End point values	aHyC	control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	7		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	17.6 (5.7 to 32.6)	6.3 (3.7 to 9.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Regulatory natural killer (NK) cells

End point title	Regulatory natural killer (NK) cells

End point description:

For each patient a percent of change in NK population was calculated.

End point type	Secondary

End point timeframe:

From the beginning of baseline period until the beginning of cross-over period.

End point values	aHyC	control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: % change				
arithmetic mean (standard error)	0.7 (± 0.3)	3.2 (± 0.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

In both arms median Overall survival was not reached at the time off cut-off date. Instead, median observation periods are given, from the diagnosis of CRPC until the cut-off date or death. However, an additional parameter was analyzed to evaluate efficacy: time-to-next-treatment (TTNT), which was significantly prolonged in aHyC patients (see also attached document: Results summary).

End point type	Secondary

End point timeframe:

From CRPC diagnosis until the cut-off date (Jan 31, 2019) or death.

End point values	aHyC	control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	7		
Units: months				
median (inter-quartile range (Q1-Q3))	42 (33.8 to 53.9)	47.9 (26.0 to 59.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
The observation period was set from the first application until 6 months after the last application in cross-over period (aHyC or placebo).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17

Reporting groups	
Reporting group title	All patients
Reporting group description:	
The reporting group consists of all patients who participated in the trial, whether or not they received the aHyC vaccine (N = 20).	

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 20 (40.00%)		
General disorders and administration site conditions			
Flu-like symptoms			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	6		
Fever			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Anemia			

subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Lymphedema			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Lyphadenopathy			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dyspnea			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rush			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Erysipelas			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Low abdominal/bladder pain			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
Frequency/urgency			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Dysuria			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		

Nocturia subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3		
Hesitancy/poor stream subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
Urinary retention subjects affected / exposed occurrences (all)	4 / 20 (20.00%) 4		
Overflow incontinence after biopsy subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
Nephrostomy dysfunction subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Transurethral resection of prostate subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
Musculoskeletal and connective tissue disorders			
Muscle pain subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported